REMARKS

Claims 1-4, 6-13, and 15-22 are now pending in this application. Claims 6 and 11-13 have been withdrawn by the Examiner. Claim 5 has been previously canceled without prejudice. Previously withdrawn claim 14 is canceled without prejudice.

Claims 1 and 7 have been revised. Claims 15-22 are new. Support for revision of claims 1 and 7 to feature "zoonosis free" may be found at least at page 2, line 2 of the application as filed. Revision of claims 1 and 7 to recite the inherent "human" thyroid stimulating hormone may be found at least in the abbreviations used in the claims, at page 4, line 11, and throughout the instant application as filed. Support for revision of claims 1 and 7 to feature "soluble" hTSHR or "soluble" hTSHR-ECD may be found at least in Examples IV and V of the application as filed.

Specification support for new claims 17, 19 and 24 featuring "hyperthyroidism" may be found at least at page 4, line 15. Specification support for new claims 18, 20 and 25 featuring "Grave's disease" may be found at least at Example V. Support for new claims 21 and 22 may be found in the original claims and throughout the application as filed.

No new matter has been introduced, and entry of the above revised claims is respectfully requested.

Alleged Rejections under 35 U.S.C. §103(a)

Claims 1-5 and 7-10 stand rejected as allegedly obvious in light of Whitelam (J. Sci. Food Agric., 68:1-9, 1995) in combination with each of Stiens et al. (Biotechnol. Prog., 2000, 16:703-709), Mullins et al. (J. Clin. Invest., 96:30-37, 1995), and Takeo et al. (EP 0719 858 A2 (1996)). Applicants have carefully reviewed the statement of the rejection and respectfully submit that no *prima facie* case of obviousness is present.

Applicants respectfully point out that the Examiner acknowledges that the general review of Whitelam et al. does not report a recombinant hTSHR polypeptide. Applicants respectfully point out that Whitelam et al. also do not report expression of a recombinant hTSHR-ECD polypeptide. Moreover, Applicants respectfully submit that the general review of Whitelam et al. does not report the conformation dependent expression and isolation of a soluble hTSHR or a soluble hTSHR-ECD polypeptide. That document also does not report or suggest a polypeptide that binds an hTSHR autoantibody from a human subject suffering from, for example, Grave's disease. Applicants respectfully submit that one of ordinary skill would have no reason to predict that a soluble hTSHR or a soluble hTSHR-ECD isolated (e.g., purified) from any

recombinant plant cell expression system would bind a naturally occurring autoantibody, with a reasonable expectation of success.

Because the feature of expressing a hTSHR extracellular domain (ECD) is not taught or suggested by Whitelam et al., one or more of the other three cited documents must do so in order to establish a *prima facie* case of anticipation. But none of them, whether each is taken alone or in any combination, teach or suggest expression of the ECD. Therefore, no *prima facie* case of obviousness is possible against claims 21 and 22, which feature ECD expression.

Whitlam et al. do not report expression of any mammalian receptor protein in a plant expression system. They also fail to teach or suggest expression of a protein with a transmembrane domain, which a skilled person would expect to cause the protein to be expressed as an integral membrane protein. But the hTSHR protein featured for expression in the claims is recognized as having a transmembrane domain as early as in 1995 as shown by the following abstract.

1: Biochem Biophys Res Commun. 1995 Jun 6;211(1):205-10.

Constitutive activation of the thyrotropin receptor by deletion of a portion of the extracellular domain.

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Mutations involving the transmembrane domain of the thyrotropin receptor (TSHR) confer constitutive activation of the receptor and can cause human diseases. Naturally occurring activating mutations identified to date are located only in the transmembrane domain of the receptor. We now report a mutant involving the extracellular domain of the TSHR which also shows constitutive activation. This mutation is missing residues 339-367 located in the C-terminal portion of the extracellular domain. When expressed in COS-7 cells, the mutated TSHR (M3B) retained similar TSH binding ability to that of the wild-type receptor. However, the basal cAMP production without TSH stimulation in COS-7 cells transfected with M3B cDNA was significantly higher than that of COS-7 cells with wild-type receptor, indicating that the mutant receptor is constitutively activated. Our results provide new insight into the mechanism of receptor activation.

PMID: 7779086 [PubMed - indexed for MEDLINE]

Because the instant claims encompass the expression of an hTSHR protein as a *soluble* polypeptide, there is the presence of unexpected results in support of the claimed invention. The expression of a protein with a transmembrane domain as a soluble protein is in contrast to Whitelam et al., who do not teach or suggest expression of any hTSHR protein as a soluble protein. This failure by Whitelam et al. is not remedied by any other cited document, whether taken alone or in any combination.

Instead of supporting the instant rejection, Whitelam et al. suggest that expression in plant cell systems have not always worked effectively for the production of immunoglobulin (see

e.g., page 5, column 2, second full paragraph, lines 1-9). Whitelam et al. report that expression of fully native mammalian cell proteins containing signal sequences leads to partially processed proteins (e.g., page 3, column 1, lines 40-45). Applicants respectfully submit that one of skill would appreciate that such partial processing could lead to non-native protein conformation, presentation of non-native antibody epitopes, and/or the inability (or reduced ability) to bind ligand and/or naturally occurring autoantibody. Further, Whitelam et al. acknowledge that efficient expression in plant cell systems is benefited by partitioning of recombinant proteins via the use of fusion proteins with plant targeting sequences. Whitlam et al. acknowledge that challenges exist for plant based expression of mammalian cell proteins (e.g., page 8, first column, last paragraph).

The above discussion of Whitelam et al. is in contrast to the feature of expressed proteins that bind a human hTSHR serum autoantibody as presented in claims 15-20. While Whitelam et al. reports expression of only partially processed proteins, the need for a fusion protein configuration, and challenges to success, the pending claims embrace the successful expression of proteins in a more native conformation that is recognized by autoantibodies without the need for a fusion protein.

Based upon the above, Applicants respectfully submit that the expression of a mammalian cell protein reported by Whitelam et al. (e.g., immunoglobulins and HSA) in transfected plants cannot be asserted as "obvious" for the expression of other proteins. In addition, Whitelam et al. do not report expression of a mammalian receptor protein from a transfected plant cell-based system. Based upon the above, Applicants respectfully submits that it is surprising and unexpected that hTSHR or hTSHR-ECD (including its native signal sequence) would be expressed and processed efficiently in a transfected plant cell. Applicants respectfully submit that the general review of Whitelam et al. could not (in the absence of hindsight) lead one of ordinary skill to a method of the instant claims, with a reasonable (or predictable) expectation of success. Thus, Applicants respectfully submit that Whitelam et al. provide no rationale by which one of skill would predictably arrive at the instant claims.

Applicants respectfully submit that Stiens et al. do not (alone or in any combination with Mullins et al. and Takeo et al.) remedy the above deficiencies of Whitlam et al. Applicants respectfully point out that Stiens et al. clearly report that expression of TSH-R is unpredictable. Stiens et al. report that TSH-R could not be effectively expressed in most expression systems tested (bacteria, yeast and insect). And when it could be expressed in animal cells (e.g., CHO and COS), it was only at very low levels. Applicants respectfully point out that Stiens et al. report the extreme difficulty of expressing sufficient amounts of functional TSH-R (e.g., with the

activity of binding a serum autoantibody and/or a ligand) in well accepted (conventional) expression systems. Applicants respectfully submit that such unsuccessful (or otherwise inefficient) expression of TSH-R in bacterial, yeast, insect and mammalian cell systems would not lead one of ordinary skill to predict that TSH-R could be expressed in a plant expression system reported by Whitelam et al., with a reasonable expectation of success.

Moreover, Applicants respectfully point out that Stiens et al. merely report optimizing fermentation conditions for growth of transfected K562 cells in a bioreactor (to overcome the low levels of expression achieved). In addition, Applicants respectfully point out that ligand binding reported by Stiens et al. is to cell surface localized TSH-R of intact K562 cells. In stark contrast, hTSHR or hTSHR-ECD of the instant claims is a soluble protein. Applicants respectfully submit that the mere optimization of bioreactor conditions for animal cell fermentation of transfected K562 cells provides no rationale (alone or in any combination with Mullins et al. and Takeo et al.) by which one of ordinary skill in the art would modify the report of Whitelam et al. to arrive at the instant claims

Applicants respectfully submit that based upon Stiens et al. (alone or in any combination with Mullins et al. and Takeo et al.) one of ordinary skill could not predict that a plant cell system would express soluble hTSHR or hTSHR-ECD. The unexpected results of the instant application provide expression of a functional hTSHR or hTSHR-ECD, in large amounts. Applicants respectfully submit that it is only with the impermissible use of hindsight reconstruction based upon the instant disclosure that the Examiner alleges the instant claims are obvious over Whitelam et al. and Stiens et al. (alone or in any combination with Mullins et al. and Takeo et al.).

Applicants respectfully submit that Mullins et al. (alone or in any combination with Stiens et al. and Takeo et al.) do not remedy the deficiencies of Whitelam et al. Similar to the report of Stiens et al., Applicants respectfully point out that Mullins et al. report the transfected EBVL animal cell-based (i.e., cell surface localized) expression of TSH-R. Applicants respectfully submit that the cell-based expression of the cell-surface localized TSH-R of Mullins et al. is distinct from the instant claims. In stark contrast, hTSHR or hTSHR-ECD of the instant claims (expressed in transfected plant cells) is a soluble protein. Since Mullins et al. and Stiens et al. (and Takeo et al. as detailed below) only report TSH-R at the surface of an animal cell, one of skill could not predict that a soluble hTSHR or soluble hTSHR-ECD would be expressed from a transfected plant cell. Moreover, the skilled person would not expect the expressed protein to bind naturally occurring hTSHR autoantibody. Thus, Applicants respectfully submit that one of ordinary skill would not look to the report of Mullins et al. (alone or in combination with Stiens et

al. and/or Takeo et al.) to modify the general review of Whitelam et al. to arrive at the instant claims with a reasonable (or predictable) expectation of success.

Applicants respectfully submit that Takeo et al. (alone or in any combination with Stiens et al. and Mullins et al.) do not remedy the deficiencies of Whitelam et al. Applicants respectfully point out that Takeo et al. report the use TSH-R within membranes prepared from thyroid tissue. In more detail, Takeo et al. report the use of transfected myeloma (animal) cells to prepare and evaluate the activity of cell surface membranes containing TSH-R. In stark contrast, the instant claims feature a soluble (i.e., supernatant) or otherwise cell membrane free hTSHR or hTSHR-ECD obtained from extracted plant parts (e.g., leaves). Thus, Applicants respectfully submit that one of ordinary skill would not look to the report of Takeo et al. (alone or in any combination with Stiens et al. and Mullins et al.) to modify the general review of Whitelam et al. to arrive at the instant claims with a reasonable (or predictable) expectation of success.

Based upon the above, Applicants respectfully submit that there is no *prima facie* case of obviousness against the rejected claims. Accordingly, this rejection is misplaced and may be properly withdrawn.

Conclusion

It is believed that the application is now in condition for allowance. Applicants request the Examiner to issue a notice of Allowance in due course. The Examiner is encouraged to contact the undersigned to further the prosecution of the present invention.

The Commissioner is authorized to charge JHK Law's Deposit Account No. **502486** for any fees required under 37 CFR § 1.16 and 1.17 and to credit any overpayment to said Deposit Account No. **502486.**

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Respectfully submitted,

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